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ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,325	ELLIOTT ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *110-114,116-118 and 120-156* is/are pending in the application.

4a) Of the above claim(s) *126-151* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *110-114,116-118,120-125 and 152-156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response submitted on 2/2/04 have been entered. Claims 115 and 119 have been canceled. Claims 110-113, 116-118, 124, 125 have been amended. Claims 152-156 are newly submitted. Claims 126-151 are withdrawn from consideration as drawn to non-elected invention. Claims 110-114, 116-118, 120-125, and 152-156 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 2/2/04 response would be addressed to the extent that they apply to current rejection.

This application contains claims (126-151) drawn to an invention nonelected without traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

The format of amendments to the claims does not comply with the Revised Amendment Practice of 37 CFR 1.121 (See OG Notice 23 September 2003). Specifically, the text of withdrawn claims (126-151) must be identified as "withdrawn" and the text of canceled claims (15, 19) must be omitted.

Claim Objections

Claim 110 is objected because the semicolon in line 8 should be deleted. Further, The phase "exposing pancreatic islet cells to nicotinamide" in step (ii) should be replaced with "exposing the harvested pancreas to nicotinamide".

Claim 117 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 117 depends from claim 116, directed to a compound that is either IGF-I or GPE, whereas claim 117 encompasses any compound that comprises GPE, thus, the scope of a dependent claim is broader than the base claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 120 is objected to because the recitation "at least one of the pancreas". Claim 120 depends from claim 110, which recites, ""harvesting the pancreas of a piglet", claim 120 is objected to because one piglet cannot have more than one pancreas.

Claim 123 is objected to because it depends from claim 110, and is drawn to further reducing the harvested pancreas mechanically. Since step (iii) of claim 110 has resulted in the isolation of pancreatic islet cells, it does not appear necessary to further reduce the pancreas mechanically or the step of 123 should follow the step (ii) of claim 110.

Claims 124 and 125 stand objected to because the term "quinalone" in the amended claims is not present in general or medical English dictionaries.

Claim 153 is objected to because the phase "exposing beta islet cells to nicotinamide" in step (ii) should be replaced with "exposing the pancreas to nicotinamide".

Claim 156 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 156 depends from claim 154, and recites the same limitation as claim 154, thus claim 156 fails to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 117 is newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in

terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The amended claim 117 recites "the compound comprises GPE". Given the broadest reasonable interpretation, the claim embraces unknown numbers of compounds that comprises an N-terminal tripeptide structure of IGF and having similar function of IGF-1. However, other than IGF-1, the specification is silent with respect to the structure of a genus of such compounds let alone the function of these compounds. Therefore, the specification fails to provide an adequate written description commensurate with the scope of the claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the numerous compounds comprising and having the function of the N-terminal tripeptide of IGF-1.

Claim 117 is newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

As indicated *supra* in the written description section, the specification fails to provide an adequate description for the numerous compounds comprising GPE. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, IGF-1 alone is insufficient to describe the genus, because from the instant disclosure, one can not envision the detailed structure of the compounds encompassed by the claims and it is unpredictable whether the compounds

will function as GPE or IGF-1. In view of the state of the art, protein chemistry is probably one of the most unpredictable areas of biotechnology. Although the polynucleotide-coding region determines amino acid sequence of the protein, it is the conformation of three-dimensional structures that allows the protein to function and carry out the messages of the genome. Thus, even though a compound other than IGF-I may contain an N-terminal tripeptide structure, it may not function as GPE because the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see *Ngo*, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). *Rudinger* (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that for peptide hormones, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "CASE TO CASE PAINSTAKING EXPERIMENTAL STUDY" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the genus of compounds comprising the N-terminal tripeptide of IGF-1 and function as GPE, because the folding and the function of the resulting polypeptide is unpredictable.

In conclusion, one cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of compounds encompassed by the claim and their function, thus would not know how to use the invention without first carrying out undue experimentation to determine which of the compounds meet claim limitation.

Accordingly, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 110, 116, and 118 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

With respect to the rejection concerning the timing of the nicotinamide treatment and whether NA could reach beta islet cells before extraction, applicants argue that the pancreas is a non-encapsulated endocrine organ and allows fluids and solutes to flow into and out of the organ. In view of the arguments and prior art of record administering nicotinamide systemically in a subject (e.g. *Nielsen et al*, US 6,225,310, column 13, lines 13-17), the rejection is now withdrawn.

With respect to beta cell exposure to IGF-I, in 2/2/04 response, applicants argue that the rejection is based on a misinterpretation of the specification and/or claim, that the specification does not suggest a reduced benefit by increasing exposure to IGF-1 for those cells from piglets furthest from full term, and the claim does not recite an increased benefit gained by increasing exposure to [IGF-1]. Applicants indicate that they do not see how such facts, even if true, would undermine the claim in terms of written description and enablement.

The arguments are fully considered but they are not persuasive. This is because the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "DURING PATENT EXAMINATION, THE

PENDING CLAIMS MUST BE 'GIVEN THEIR BROADEST REASONABLE INTERPRETATION CONSISTENT WITH THE SPECIFICATION'. *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 Fed. Cir. 2000" (MPEP 2111). In the instant case, the claims are drawn to a method of preparing xenotransplantable porcine pancreatic islet cells, any step in the method must be consistent with and promoting/beneficial to the goal of the method. Thus, even though the claims do not recite "increased benefit gained", given the broadest reasonable interpretation that is consistent with the specification, the method step should fulfill the purpose of preserving xenotransplantable pancreatic beta cells, or else the specification fails to teach the purpose/utility of increasing the amount of compound treating islets from a piglet further from full-term gestation. Accordingly, the claim has not been misinterpreted but evaluated by the standard provided in the MPEP, and the facts do matter for the sake of enablement, i.e. the specification fails to disclose that increased amount of IGF-1 would be beneficial to the pancreatic beta cells furthest from full term gestation, and it teaches away by the statement, "*No further benefit was achieved by increasing the concentration of IgF-1*" (page 17, lines 19-20). This opinion was also reflected in the previous claim 119, now canceled, which states "*the exposure to IGF-1 is unrelated to their relationship with full term gestation*". Applicants are reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Accordingly, the rejection stands.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 110-114, 116-118, 120-125, 153-156 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claim 110 recites "exposing pancreatic islet cells to nicotinamide" in step (ii). However, since there is no limitation on the recited islet cells with respect to their source and relationship with the pancreas of step (i) and it appears that the islet cells have not been extracted from the harvested pancreas until step (iii), thus, the source of the islet cells of step (ii) is unclear, and the metes and bounds of the claim is uncertain.

Claim 116 recites the limitation, "the step of treating the islets". There is insufficient antecedent basis for this limitation in the claim. It is unclear which step the claim refers to, thus, the metes and bounds of the claims are uncertain.

Claim 120 recites the limitation, "the step of subjecting...". There is insufficient antecedent basis for this limitation in the claim. It is unclear which step the claim refers to, thus, the metes and bounds of the claims are uncertain.

Claim 153 recites "exposing beta islet cells to nicotinamide" in step (ii). However, since there is no limitation on the recited islet cells with respect to their source and relationship with the pancreas and it appears that the islet cells have not been extracted from the harvested pancreas until step (iii), thus, the source of the islet cells of step (ii) is unclear, and the metes and bounds of the claim is uncertain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

The prior rejection of claims 110, 111, 113, 115, 120 under 35 U.S.C. 102(b) as being anticipated by *Rayat et al* (Diabetes 1998;47:1406-11) is withdrawn in view of claim amendment.

Claims 110, 111, 120, 123 stand rejected under 35 U.S.C. 102(e) as being anticipated by *Elliott* (6,146,653 or 6,090,400), and the rejection applies to new claims 152-156 for reasons of record and following.

The subject matter of new claims 152-156 are encompassed by the original claim 110, and fully disclosed in the cited patent.

Applicants indicated that this rejection under 35 U.S.C. 102(e) might be overcome by a showing under 37 CFR 1.132, and are willing to supply such a declaration at a future time.

Until then, the rejection stands for reasons of record.

Claims 110, 111, 120, 123 stand rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter, and the rejection applies to new claims 152-156 for reasons of record and following.

Applicants indicated that this rejection might be overcome by a showing under 37 CFR 1.132, and are willing to supply such a declaration at a future time.

Until then, the rejection stands for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

In view of the claim amendment, the rejections in this section have been modified as following.

Claims 110, 111, 113, 120, 152-156 are rejected under 35 U.S.C. 103(a) as being obvious over *Rayat et al* (Diabetes 1998;47:1406-11), in view of *Nielsen et al* (US 6,225,310), and as evidenced by *Kallmann et al* (Life Sciences 1992;51;671-8) and *Elliott et al* (Ann N Y Acad Sci. 1993 Nov 30;696:333-41).

Rayat et al teach a method of preparing porcine islet cells as potential source for transplantation in humans (abstract) comprising harvesting the pancreas from neonatal piglets at 1-3 days, extracting pancreatic islet beta cells, and culturing the islet cells in the presence of nicotinamide and bovine serum albumin (trauma-protecting agent) under sterile condition (free of microbial by including penicillin and streptomycin in the medium, paragraph bridging pages 1406-7). *Rayat et al* go on to teach that beta cells obtained from adult porcine are fragile and difficult to maintain in tissue culture and report the studies in the art regarding use of neonatal and fetal pancreas to obtain beta cells (e.g. 1st paragraph, page 1406, and Discussion). Thus the teachings of *Rayat et al* establish that the prior art recognized the advantages of using fetal and neonatal tissue for obtaining beta islet cells and including nicotinamide in the preparative process.

The teaching of *Rayat et al* differs from instant claims in that the nicotinamide (NA) was in the culture medium after extraction of beta cells, not before or simultaneously at the time of extraction. *Nielsen et al* supplement *Rayat et al* by teaching the mechnisms and clinical use of nicotinamide in protecting the pancreatic beta cells. *Nielsen et al* teach that NA could inhibit cytotoxicity caused by nitro oxide

and other free radicals on beta cells (which are often seen in trauma) such as evidenced by *Kallmann et al*, as well as influence several of the putative intracellular molecular events following immune attack on the beta cells such as evidenced by *Elliott et al*. *Nielsen et al* teach that both animal and human studies have shown beneficial effects of NA on beta cells in diabetes patients (column 13, lines 13-34). While *Nielsen et al* do not particularly teach the cell preparation process, the reasonably skilled artisan would have been motivated to include NA in any stage of the harvesting, extraction, and cultivation given the many known beneficial effects of NA on pancreatic beta cells, particularly preventing the minor traumatic effect on islet cells caused by mechanical manipulation during preparation.

Therefore, in view of the protective effect of NA on beta islet cells as taught by *Nielsen et al*, it would have been *prima facie* obvious to the skilled artisan at the time of filing to include NA at any stage of preparation in the method taught by *Rayat et al* for maximal protective effect. Further, based on successful use of NA in protecting beta cells and treating diabetes as taught by *Nielsen et al*, the skilled artisan would have had a reasonable expectation of success in using such for preparing pancreatic islet cells for xenotransplantation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the 2/2/04 response, Applicants indicated that claim 110 has been amended, Rayat et al teach exposing the islet cells to nicotinamide only after the extraction step, not before as now claimed. In response, the rejection has been modified accordingly to include the teaching of *Nielsen et al* showing that based on the art-known protective

effect of NA on pancreatic beta cells, it would have been obvious to expose the cells with NA at either before or after the extraction of pancreatic islet cells to achieve maximal protection.

Claim 112 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11), and *Nielsen et al* (US 6,225,310) as applied to claims 110, 111, 113, 120, 152-156 above, and further in view of *Brandhorst et al* (Transplant 1999;68:355-61, IDS).

Claim 112 is drawn to using human liberase in the step of islet cell extraction. *Rayat et al* use collagenase but not Liberase.

Brandhorst et al supplement the teaching of *Rayat et al* and *Nielsen et al* by disclosing the benefit of substituting collagenase with Liberase. *Brandhorst et al* teach that a barrier for successful islet isolation is the intrinsic fragility of islets during pancreas digestion and using human Liberase could double the yield of islet cells compared to collagenase (abstract), "LOW-TEMPERATURE DIGESTION OF PORCINE PANCREATA USING LIBERASE HI COULD SERVE AS AN ESSENTIAL PREREQUISITE FOR SUCCESSFUL 1:1 XENOTRANSPLANTATION OF PIG ISLETS".

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al* and *Nielsen et a* by simply substituting collagenase with Liberase in pancreas harvesting and digestion as taught by *Brandhorst et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it

could enhance the yields of islet cells substantially. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the 2/2/04 response, Applicant asserts that unexpected and beneficial results described in the present application taught much greater yields of islet cells can be obtained than would be expected in view of the *Brandhorst et al* disclosure.

The argument has been fully considered but found not persuasive. This is because *Brandhorst et al* has taught the benefit of using liberase in adult pig pancreas as compared to collagenase, and has provided evidence of success. Accordingly, when following the suggested step, applying the liberase on porcine neonatal or fetal cells, a higher level of beta cells yields should have been reasonably expected since it is known the neonatal and fetal pancreases are less fragile compared to the adult pancreas as taught by *Rayat et al.* Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., higher levels of beta cell yields) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Thus, the claimed invention as a whole is obvious over the combined teachings of the cited prior art.

Claims 114, 116, 123 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310) as

applied to claims 110, 111, 113, 120, 152-156 above, and further in view of *Clark et al* (Endocrinol 1990;126:1895-1903) and *Maysinger et al* (CA 2,216,055, IDS).

The claims are drawn to culturing the obtained islet cells in the presence of IGF-1, and human serum albumin (HAS), and extracting the islet cells by mechanical means in the presence of an islet trauma-protecting agent. *Rayat et al* and *Nielsen et al* do not teach these steps in the method of islet cell preparation.

Clark et al supplement the teachings of *Rayat et al* and *Nielsen et al* by developing a defined medium comprising IGF-I and HAS for culturing islet cells of rats (abstract). They teach the need for developing the medium and the function of the components in the medium for long term sustained culture of adult as well as fetal islet cells (Introduction, and table 1). For islet cell extraction, they teach terminating the trypsin digestion with fetal bovine serum-containing medium, and obtaining the islet cells by aspiration of islets through stainless steel cannulae (mechanically reducing the harvested pancreas). Because the FBS generally promotes cell growth, and protects cell membrane, thus, is considered as trauma preventing agents. *Clark et al* teach cultures for rat cells, not porcine.

Maysinger et al teach culturing mammalian islet cells in general in the presence of IGF-I (page 4, line 30), and including one or more growth factors having anti-apoptosis effect on islet cells (trauma preventing agent, abstract). Evidently, the skilled artisan does not discriminate among the species of the mammalian for culture conditions of islet cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al, Nielsen et al, Clark et al*, and *Maysinger et al* by simply including IGF-I and HAS and adding trauma protecting agent during the mechanical disassociation of pancreas with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the modified method enhances the viability and sustained survival of ex vivo cultured islet cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants did not provide specific arguments for this rejection, thus, for reasons of record and set forth above, the rejection stands.

Claims 116 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11), *Nielsen et al* (US 6,225,310), *Clark et al* (Endocrinol 1990;126:1895-1903) and *Maysinger et al* (CA 2,216,055, IDS) as applied to claims 110, 113, 114, 116, 120, 123, 152-156 above, and further in view of *Saura et al* (Neuroendocrinol 1999 Jan 18;161-4).

Claims 116 and 117 are drawn to treating islet cells with GPE.

The combined teachings of *Rayat et al, Nielsen et al, Clark et al*, and *Maysinger et al* do not disclose that the N-terminal tripeptide of IGF-I would have the biological activity of the full length IGF-I.

However, before the instant effective filing date, *Saura et al* teach that some of the biological effects of IGF-1 is mediated by the N-terminal tripeptide fragment (GPE),

and confirm the GPE does have the biological activity of full length IGF-I in the brain tissue (see particularly abstract § Introduction).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al, Clark et al*, and *Maysinger et al* by simply substituting full length IGF-I with the GPE tripeptide with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it has been proven that GPE has the biological activity of IGF-I and has a smaller size, thus easier for cell delivery, and providing additional means for similar biological activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants argue *Saura et al* teach that GPE has the activity of IGF-1 in brain tissue, such knowledge would not obviously lead one of skill in the art for using such in preparing islet cells.

In response, *Saura et al* do not limit the teaching in brain cells, and teach that the IGF biological effects in general are mediated by the GPE, thus, the GPE effect is defined by the biological function of IGF-1. Since IGF-1 functions in both islet cells and brain cells, there is a reasonable expectation of success when substituting IGF-1 with GPE given the confirmation provided by *Saura et al*. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Claims 121 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310), as applied to claims 110, 111, 113, 120, 152-156 above, and further in view of *Pu et al* (Brit J Pharmacol 1996;118:1072-8).

Claims 121 and 122 are drawn to treating pancreas or islets with lignocaine as the trauma-protecting agent in the process of preparation. *Rayat et al and Nielsen et al* fail to teach using lignocaine.

Pu et al teach that addition of lignocaine in isolated rabbit heart tissue culture could restore the contractility of myocardiocytes after minor traumatic injury (myocardial contusion), and thus lignocaine could be used as a therapeutic agent for tissue recovery from minor trauma (abstract, and § 5). Here, the contractibility of myocardiac cells is a measurement for health status of these cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Rayat et al,* and *Pu et al* by including lignocaine in the pancreas harvesting and extracting process with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the lignocaine has been proven effective in protecting cells from minor injury. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants assert that the knowledge that lignocaine can act to restore heart contractions would in no way suggest to one of skill in the art that this compound would be of any use in maintaining and transplanting pancreatic islet cells.

In response, as an initial matter, the contractibility of heart cells is a measurement for health status of these cells, even though such status in pancreatic beta cells is not measured by the contraction, the protective effect on myocytes reflects general beneficial effect of lignocaine. *Pu et al* have extend the observation of lignocaine in protecting heart cells to apply to all tissue recovery from minor trauma, and the trauma due to tissue harvesting and extraction certainly fall within the category of minor trauma. *Pu et al* suggested that although further confirmation study is needed, lignocaine is likely to promising therapeutic intervention (abstract, § 5). Thus, in the absence of evidence to the contrary, an expectation of success is reasonable. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Claims 124 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rayat et al* (Diabetes 1998;47:1406-11) and *Nielsen et al* (US 6,225,310), as applied to claims 110, 111, 113, 120, 152-156 above, and further in view of *Boss et al* (US 6,432,710) and *Champion et al* (US 4,850,993).

Claims 124 and 125 are drawn to culturing islet cells in the presence of quinoline antibiotics, preferably ciproxin. *Rayat et al* use penicillin and streptomycin, but not quinoline.

However, before the instant effective filing date, *Boss et al* teach that quinoline antibiotics is useful in preventing mycoplasmal contamination (column 13, line 64-

column 14, line 4). *Champion et al* teach that ciproflaxin (ciproxin) belongs to quinoline antibiotics (column 2, line 14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Rayat et al* and *Nielsen et al* by including ciproxin in the culture medium for preventing mycoplasmal contamination with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because mycoplasmal contamination is a concern for many cell culture laboratories and ciproxin has been proven effective for prevention. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants refer to the argument as presented in the rejection of claim 110, which has been addressed above, thus, will not be reiterated here.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 110, 111, 120, and 123 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 13, and 14 of U.S. Patent No. 6,146,653.

Applicants argue that claims as amended are significantly distinct from those of the cited patent, and any such claims would not be co-extensive in scope with those of the previously issued patent.

In response, the claims of the cited patent are drawn to a preparation of porcine islet cells for xenotransplantation prepared by the presently claimed method, wherein claim 11 recites "said islets ...[have] been treated during preparative procedures with nicotinamide", which encompasses exposing islets to NA at any stage of the preparative procedure, and is not limited to before or after the extraction step.

Accordingly, the claims in the copending and the present application are obvious variants, and the inventions as claimed are co-extensive.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.

Q. Janice Li
Patent Examiner
Art Unit 1632

JANICE LI
PATENT EXAMINER

QJL
May 17, 2004